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Africa Centres for Disease Control and Prevention (Africa CDC)

Guidance on Emergency Expedited Regulatory Authorisation and Access to COVID-19 Vaccines in Africa

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Taking the whole of Africa approach to fighting the COVID-19 pandemic has and will continue to require coordinated efforts from multiple stakeholders from across the continent. Africa CDC would like to acknowledge the deep partnership and continued support of AUDA-NEPAD, AVAREF, WHO AFRO, the Bill and Melinda Gates Foundation and the Mastercard Foundation. These partners have helped to shape and drive the continent's strategic response to the COVID-19 pandemic and have offered support to ensure the continent receives a fair and equitable share of the COVID-19 vaccine without delay.

We look forward to continuing and deepening our partnership for the benefit of the public health of Africa.

1. Background and purpose of this document

To prevent and contribute to reducing COVID-19 transmission and deaths while at the same time protecting African economies and societies requires the successful immunisation of a critical mass of the African population with safe and efficacious COVID-19 vaccines that are quality-assured to international standards.

The COVID-19 Vaccine Development and Access Strategy (Vaccine Strategy) aims to immunise at least 60% of the African population with vaccines that have been proven safe and efficacious and are quality-assured to international standards to develop "herd immunity." This target is based on scientific research showing that when a significant part of a population is immune to an infectious disease, the virus will have a much harder time infecting susceptible individuals, as the risk of contacting an infected individual for the non-vaccinated population will be diminished. This "herd immunity" will thus help mitigate further outbreaks of the disease. The exact percentage needed to achieve this mitigation depends on several factors such as population density; a minimum of 60% is the current view given the situation in Africa (for more details, please refer to Annex 1).

The African Union Bureau of the Assembly Heads of State and Government, chaired by His Excellency President Cyril Ramaphosa of South Africa, endorsed the continental vaccine strategy on 20 August 2020.

Demand for COVID-19 vaccines in 2021 is expected to be immense – and will very likely exceed global supply. Around 8.4 billion doses have already been pre-ordered as of January 2021. This would be enough to immunise approximately 50% of the world population, considering that most vaccines require two doses. However, doses will not be allocated evenly among countries. Many high-income countries have already pre-ordered several doses above what they require to immunise their entire population (as they have ordered from multiple manufacturers, not knowing which vaccine(s) might be effective), while the number of doses committed to most African countries are between 5 and 10 percent of their population[1],[2]. The majority of low-middle income countries (LMICs) are reliant on the COVAX facility.

In the global race to secure supply, country prioritisation by manufacturers of COVID-19 vaccines will partly be made according to country readiness – key components of which are an efficient regulatory environment, streamlined decision-making processes, and a delivery programme that is fit for purpose. It is thus incumbent upon Member States to ensure that these processes are established and functioning optimally for the benefit of the public health of the continent.

[1]"Tracking the Coronavirus Vaccines that will end the Pandemic", Bloomberg, 21 January 2021 (https://www.bloomberg.com/graphics/covid-vaccine-tracker-global-distribution)
[2]Excluding vaccines obtained through COVAX

2. Long-term drug regulatory harmonisation initiatives in Africa

When countries work together on regulatory approvals, especially in regional economic communities (RECs), significant progress can be made to reduce the time required for regulatory approvals of medicines crucial for addressing public health priorities. The African Medical Regulatory Harmonization (AMRH) initiative, established in 2009, aims to address this issue by shifting the continent from a base of 55 national regulatory authorities making individual decisions on medical products to a more collaborative and regional approach using coordinated networks of national regulators for assessment purposes. For example, the East African Community (EAC) Medicines Regulatory Harmonization (MRH) initiative has improved reliance and work-sharing (e.g. medicines evaluation and registration, GMP inspections, pharmacovigilance) – a study conducted by Janssen saw a 40-60 percent reduction in national approval time for selected branded medicines through the EAC's joint dossier assessment[3]. Similarly, the South African Development Community (SADC) has set up a harmonization initiative called ZaZiBoNa[4]. Initial results show that the joint review and subsequent national approval processes have resulted in shorter timelines for marketing authorisation (median 9–10 months) compared to those for products assessed by individual countries. While the recommendations in this paper are primarily aimed to tactically address the main regulatory process challenges to the safe and efficient introduction of COVID-19 vaccines in the African continent, they should be seen as complementary to the broader medical products scientific technical harmonisation and regulatory process optimisation agenda in Africa.

Regulatory authorisations play a crucial role in access. On the one hand, they are critical to ensuring that the vaccines used are safe, quality-controlled and efficacious. On the other hand, they can cause delays in access to the vaccines. Hence, the purpose of this guidance is to advise on emergency expedited regulatory authorization procedures that provide the required checks without causing unnecessary delays. The guidance builds on the prior work and expertise of the WHO's African Vaccine Regulatory Forum (AVAREF) and AUDA-NEPAD coordinated African Medicines Regulatory Harmonization (AMRH), as well as lessons learned from the Ebola vaccine development and distribution process (for detailed lessons learned, please refer to Annex 2). It is intended to inform and guide RECs, individual countries and sponsors on the critical elements of emergency preparedness in order to ensure that the ethical and regulatory considerations safeguard public health in emergency situations and do not constitute a barrier to access.

[3]Ndomondo-Sigonda, Margareth, et al. "The African medicines regulatory harmonization initiative: progress to date." Medical Research Archives 6.2 (2018).
[4]Sithole, T., Mahlangu, G., Salek, S., & Walker, S. (2020). Evaluating the Success of ZaZiBoNa, the Southern African Development Community Collaborative Medicines Registration Initiative. Therapeutic Innovation & Regulatory Science, 1-11.

This document should be used together with the provisions of WHO's Technical Report Series on review of clinical trials, WHO Technical Report Series No 924 - Guidelines on Clinical Evaluation of Vaccines: Regulatory Expectations; AVAREF's guideline for joint and assisted reviews of clinical trial applications for national regulatory authorities (NRAS) and ethics committees (ECC); WHO TRS No 1004–Guideline on Regulatory Preparedness for Provision of Marketing Authorization of Human Pandemic Influenza Vaccines in Non-vaccine Producing Countries; WHO Emergency Use Assessment and Listing Procedure (EUAL) for candidate vaccines for use in the context of a public health emergency; and WHO Guidance on developing deployment and vaccination plans for COVID-19 vaccines.

Guidance on emergency expedited regulatory authorisation and access to ensure preparedness for COVID-19 vaccines in Africa

Based on interviews of a large group of stakeholders from the Ministries of Health (MoHs), NRAs, pharmaceutical companies, multilateral entities, technical experts and others, as well as experience from Ebola vaccine development and deployment, we have identified the potential barriers to the safe and efficient introduction of COVID-19 vaccines on the African continent. Based on those barriers, we provide the following guidance to African Union Member States:

- **Endorse the following frameworks for the market authorisation of vaccines according to three major scenarios which should be prioritised for regulatory review in the following order:**
  - **Scenario 1, for vaccines becoming available which have received WHO EUL/PQ approval:**
    - AVAREF-led post-EUL joint review process based on the Regional Economic Communities mechanism: enter reliance agreement and commit to country-level emergency use or marketing authorisation decision based on AVAREF-led recommendation (targeting local NRA emergency use or marketing authorisation within **15 working days from EUL/PQ approval by WHO**).
    - Countries are permitted to waive the AVAREF-led joint review process and commit to reliance directly on the WHO EUL process (targeting local NRA emergency use or marketing authorisation within **15 working days from EUL/PQ approval by WHO**).
    - AVAREF, following determination by COVAX of countries to be targeted with specific vaccines, will convene joint session with these countries to perform an abridged review of the EUL decision. WHO-Geneva will secure the approval of the manufacturer to share the EUL dossier submitted to WHO as well as the EUL assessment report.

- **Scenario 2, for vaccines becoming available that have received approval from one or several Stringent Regulatory Authorities (SRAs)[5],** but not yet through WHO EUL/PQ.

  - The taskforce will develop a guidance on a **standardised SRA reliance framework** for African NRAs – critically, this process will be conducted through the Regional Economic Communities.

  - In addition, the taskforce will convene a vaccine dossier review Expert Advisory Group made up of the most preeminent technical experts on regulatory assessment from within and outside the continent to review dossiers of COVID-19 vaccines which are approved by SRAs. This working group will share findings and results of the **abridged** review with the Regional Economic Communities to expedite regulatory reviews and advance the principles of reliance and work sharing.

  - RECs and NRAs must ensure that the vaccine which is approved in-country is the **exact same version** as that which received approval by the SRA (for example, AstraZeneca's vaccine will have multiple versions: SII, SK Chemicals and others).

  - This will be an abridged review of the dossier once a request to use a specific vaccine, which meets the definition for scenario 2, is submitted to at least one country within a REC. Once the manufacturer files with any country in Africa for a vaccine that is not yet WHO EUL'ed but SRA approved, AVAREF will engage with the manufacturer to understand their launch plans, and ensure those countries are included in the abridged joint review.

- **Scenario 3, for vaccines becoming available that have received neither of the above:**

  - Leverage existing collaborations among countries and information sharing through existing regional harmonization networks and processes. Recommendation from regional networks/body (e.g. EAC, Zazibona, ECOWAS) can be used for national decision-making processes.

  - In addition, the taskforce will convene a dossier review Expert Advisory Group made up of the most preeminent technical experts on regulatory review from within and outside the continent to review dossiers of COVID-19 vaccines which have not been reviewed by WHO EUL/PQ or an SRA. This working group will share findings and results of the review with the Regional Economic Communities to expedite regulatory reviews and advance the principles of reliance and work sharing.

[5]List of WHO-approved Stringent Regulatory Authorities available at: https://www.who.int/medicines/regulation/sras/en/

- **Ensure that the following minimum requirements are met by vaccine developers:** Phase III safety and efficacy data and Severe Adverse Events (SAEs) comprehensively monitored and tracked.

- **Encourage vaccine manufacturers of such vaccine products to seek approval from WHO EUL/PQ and/or Stringent Regulatory Authorities**

- Critically, if a vaccine is currently undergoing approval processes through WHO EUL/PQ or by an SRA, then RECs and NRAs should await the outcome of the process before making a regulatory decision. A list of vaccines currently under assessment by WHO EUL/PQ is available at this link.

    - Importantly, all NRAs should waive the requirement for tailored dossiers and should accept the same dossiers issued to WHO EUL/PQ (scenario 1) and/or SRAs (scenario 2).

- **Increase reliance on multilateral organisations and their frameworks by:**

    - Adopting WHO generic label format for all COVID-19 vaccines (granting NRA approval for local use).

    - Adopting WHO product use policy statement(s) on vaccine use (waiving requirements for country-specific use policy statements).

    - Waiving the requirement for CoPP for all versions of products that are obtained via the COVAX facility and/or that have SRA authorisation and/or WHO EUL/PQ listing.

    - Waving the requirement for in-country lot release testing as part of the authorisation process (and directing local laboratory capacity towards field testing to detect substandard or falsified vaccines) for all products received through the COVAX facility and/or that have SRA authorisation and/or WHO EUL or PQ listing. Instead, reliance can be placed on manufacturer's and manufacturing country NRA lot testing results submitted to WHO and local ML3/4 lot release mandated under the WHO EUL/PQ process.

    - For COVAX-procured vaccines: follow COVAX centralized manufacturer indemnification process.

- **Rely on the AMRH, AVAREF and the Africa CDC to implement critical processes in-country**, including:

    - A database of severe adverse events (SAEs) for emergency use to be established. In addition, guidance based on an ART scientific panel will be released on the requirements for Phase IV trials.

- African Union Smart Safety Surveillance (AU-3S) programme and existing national pharmacovigilance systems, utilising shared tools (i.e. immunisation worker app) for safety data collection, and relying on analysis of adverse events produced by the joint-country safety advisory committees.
- Expedited issuance of import permits for COVID-19 vaccines to expedite customs clearance (targeting decisions within less than 24 hours).
- Expedited process ensuring that approved vaccines are rapidly added to local formulary lists.
- If needed: manufacturer indemnification for non-COVAX vaccine candidates based on a standardised set of criteria.

- **Take action to ensure the full implementation of the recommended frameworks and processes:**
  - Transparent engagement and follow-up with the Africa Regulatory Taskforce.
  - Follow-up with all internal stakeholders to ensure translation of the commitment into the required laws, policies and processes or handled through emergency ministerial or presidential decree, if needed.
  - Communication to and training of key personnel, for example, in national regulatory agencies, customs personnel and port officials, supply chain agencies.
  - Allocation of sufficient human and financial resources to the Ministries of Health and NRAs, for them to draw upon flexibly and quickly to develop and perform trainings, get additional guidance and build surge capacity for the response.

It is important to note that the above guidance is focused, first and foremost, on ensuring that any COVID-19 vaccine that is approved by African NRAs meets the highest standards of international quality, safety and efficacy. The pool of potential vaccines which meet the highest standards should then be further examined based on public health recommendations on vaccine use made by WHO's Strategic Advisory Group of Experts on Immunization.

3. Conclusion

As discussed in this guidance document, addressing regulatory challenges is one of the keys to ensure that the African continent is not handicapped in its efforts to help mitigate the impact of the pandemic as quickly as possible. In addition, the processes for vaccine procurement, importation, transportation and distribution must also be addressed, while maintaining international standards of safety, efficacy, and quality. To facilitate this process, ACDC, AVAREF and AUDA-NEPAD have developed a joint plan to engage and support key stakeholders. This includes two main components: a series of engagements with representatives from member states and new sets of guidance.

After the general convening with all 55 Member States, there will be follow-up engagements to ensure initiatives are cascaded to each country's relevant institutions, as well as one-on-one meetings for tailored support. African Union, WHO/AVAREF, AUDA-NEPAD will support the countries to meet emergency timelines for regulatory review and approval of COVID-19 vaccines using the reliance principle to minimise delays. One way this will be actioned is through the release of further guidance on three main topics: decision-making processes around in-country vaccine authorisation, indemnification procedures and regulatory process optimisation.

To ensure that these efforts succeed in the mission of optimising the African regulatory environment in time to help resolve this public health emergency as quickly as other areas of the world, we ask all Member States to adopt an active and collaborative role in this common effort and commit to the recommended actions.

Annex 1:
Details on the African Union COVID-19 vaccine development and access strategy

The COVID-19 Vaccine Development and Access Strategy (Vaccine Strategy), endorsed by the African Union (AU) Bureau of Heads of State and Government on 20 August 2020, was developed by the Africa Centres for Disease Control and Prevention (Africa CDC) in alignment with the Africa Joint Continental Strategy for COVID-19 Outbreak. It draws on the expertise of more than 3000 political leaders and technical experts. Africa CDC convened on 24-25 June to discuss COVID-19 vaccine needs on the continent and regional opportunities for driving development, manufacture, distribution and uptake.

The Vaccine Strategy aims to immunise at least 60 per cent of the African population with vaccines that have been proven safe and efficacious to create "herd immunity." This target reflects scientific research showing that when a significant part of a population is immune to an infectious disease. "Herd immunity" will thus avoid further outbreaks of the disease. The exact percentage needed to achieve this protection varies based on the condition, and factors such as population density; a minimum of 60% is the current view given the situation in Africa.

The Vaccine Strategy contains three key objectives:

i. **Accelerate African involvement in the clinical development of a vaccine** – driven by the Africa CDC Consortium for COVID-19 Vaccine Clinical Trials (CONCVACT), which facilitates the initiation of trials, strengthens critical enablers and supports vaccine clinical trial sites across all African sub-regions.

ii. **Ensure African countries can access a sufficient share of the global vaccine supply** – achieved in parts through AU Member States' membership in the COVAX facility, which is planning to procure and equitably distribute vaccine doses to cover 20 per cent of the participating countries' population. In order to ensure 60 per cent immunity, His Excellency, President Cyril Ramaphosa, on 7 November 2020 established the COVID-19 African Vaccine Acquisition Task Team (AVATT) to support the financing and acquisition of additional doses needed.

iii. **Remove barriers to widespread delivery and uptake of effective and quality assured vaccines across Africa** – addressed by Africa CDC in collaboration with key partners including the World Health Organization's Regional Offices for Africa and for the Eastern Mediterranean, the AU'S AUDA as well as UNICEF and other COVAX partners and the World Bank. Ensuring that the vaccines, once available and procured, can be swiftly and efficiently provided to recipients in Africa will require a collaborative and focused effort on the part of the Member States. Each will have to ensure the necessary streamlined regulatory and importation processes and approvals are in place, drive community engagement and communication on the vaccine and build delivery readiness from a strategic, organisational and logistics perspective.

Annex 2:
Lessons learned from Ebola vaccine development and distribution

Reviewing the key lessons learnt from the Ebola vaccine development and distribution process demonstrates the criticality of regulatory processes and requirements.

Sources of efficiency in the Ebola vaccine development and distribution process

- **Convenings and communication among manufacturers, ethical review committees, regulators, multilaterals and other public health institutions:** These allowed for more efficient information sharing and joint review of available data on candidate vaccines, therefore expediting time to approval[1]. An example of this was the AVAREF African Vaccine Regulatory Forum held in Pretoria, South Africa, which brought together the three vaccine candidate developers (i.e., Merck SDC, Johnson and Johnson and GlaxoSmithKline), ethics committees, regulators and other involved stakeholders.
- **Multilateral fast tracked processes:** WHO HQ, in collaboration with AVAREF and the EMA, developed an innovative facilitated process for decision making on acceptability of the vaccine for registration. This allowed for simultaneous submissions to EMA, WHO-PQ and African NRAs, with EMA acting as the reference authority. This led to the issuance of a Marketing Authorisation by the European Commission and the Pre-Qualification by the WHO within three days from the positive opinion of EMA, with NRAs starting to approve the vaccine within a month after PQ listing[2].

Sources of delays in the Ebola vaccine development and distribution process

- **Special vaccine import permits and handling requirements for recombinant vaccines:** These special procedures required due to the "dual use" of the candidate vaccine were not anticipated in advance and led to delays and extra costs. This demonstrates the importance of early stakeholder engagement to ensure regulatory preparedness[2].
- **Country-specific labelling and packaging**: The country-level requirements led to an increase in non-value adding steps (e.g., shipment of samples) and supply chain issues for the manufacturers. This demonstrated how heterogeneous requirements counter the goal of speed and cost-efficiency relevant to emergency preparedness[2].
- **Modular requirements for additional data:** During the authorisation process, many countries submitted requests for several pieces of very detailed informational requests from the vaccine developer, above and beyond what would normally be considered in authorisation processes, e.g. for EUL/PQ by the WHO, creating significant delays.

- **Similar requests for additional information:** Many requests for similar pieces of information by different countries created bottlenecks on the manufacturer's side, meaning that a decision was taken to wait until all requests had been submitted, and consolidate before following up, in order to avoid duplication of activities. This demonstrates that efficiencies could be gained by cross-country alignment before the submission of additional data requests and assuring that add data requests are indeed value-added to regulatory decision-making, especially in the context of regulatory decision-making based on reliance.[7]

Final approval of Merck's Ervebo Ebola vaccine (rVSV-ZEBOV) was granted in December 2019, just over five years after the start of Phase I clinical trials. Moreover, at the time of approval, 300,000 people had already been vaccinated in the Democratic Republic of Congo (in response to the 2018-2019 outbreak). While this was a significant advancement from the 10 to 15 years it typically takes for vaccines to complete the process[6], given the global supply challenges, Africa will need to improve its regulatory readiness by another order of magnitude to realistically compete for the scarce global supply of the COVID-19 vaccine, especially in 2021 when manufacturers will still be ramping up production. The sources of efficiency in the Ebola vaccine authorisation process (see callout box: "Sources of Efficiency in the Ebola Vaccine Development and Distribution Process") could be replicated for COVID-19 vaccine candidates – indeed, pre-emptive and committed actions should be taken to avoid the sources of delays (see callout box: "Sources of Delays in the Ebola Vaccine Development and Distribution Process).

[6]COVID-19 / Lessons from MSD's Ebola Vaccine Development: Balancing Ambition with Reality, Pharma Boardroom, accessed on 02/12/2020

Annex 3:

Regulatory barriers to the introduction of COVID-19 vaccines in the African continent

There are currently 14 COVID-19 vaccine candidates in Phase III clinical trials, with seven vaccines[7] already approved by certain national authorities for limited use[8] and one that has been Emergency Use Listed by the WHO. Upon submission of proper dossier with requisite data, many of these vaccines will be listed through the WHO EUL and/or Stringent Regulatory Authorities (SRAs). These bodies are using emergency use authorisation procedures given the public health emergency. A demonstration of this is the granting of emergency use authorisation for the Pfizer-BioNTech's C vaccine by the MHRA on 2 December 2020[9] followed by emergency use authorisation by the US Food and Drug Administration and conditional authorisation by the European Union. Research shows that, historically in more routine circumstances, once vaccines are authorised by SRAs or listed by the WHO, their final authorisation in Sub-Saharan African countries can take up to 9 years[10]. It is therefore essential that African countries continue to optimise their regulatory processes to assure a fit-for-purpose process for the COVID vaccines.

While value-added, fit-for-purpose decision-making is the goal of this initiative, it is critical to underline that speed cannot come at the expense of appropriate reviews and informed decision-making. Vaccines that meet international standards of safety, efficacy, and quality and that are appropriate for African health care facilities are non-negotiable prerequisites for any vaccine to be used on the African continent. It is, therefore, essential that the African Union Member States use only such vaccines in large-scale roll-outs that have been approved through an established multi-stakeholder process, such as authorisations by an SRA or the WHO EUL or PQ listing process.

Based on interviews of a large group of stakeholders (Ministries of Health (MoHs), NRAs, pharmaceutical companies, multilateral entities, and technical experts), the most critical national barriers for final regulatory decision making on vaccine authorisation are:

Vaccine evaluation and approval

The set of barriers related to the in-country evaluation of a vaccine (i.e. immediately after SRA authorisation and/or WHO EUL or PQ listing before its national authorisation are outlined below:

[7]At the time of writing, the vaccines approved for limited use are: CanSinoBIO – China, Sinopharm – UAE, Sinovac (2 vaccines)– China, BEKTOP – Russia, Gamaleya – Russia, Pfizer – United Kingdom
[8]https://www.nytimes.com/interactive/2020/science/coronavirus-vaccine-tracker.html
[9]https://www.nbcnews.com/news/world/u-k-becomes-first-country-approve-pfizer-biontech-covid-19-n1249651
[10]Ahonkhai, V., Martins, S. F., Portet, A., Lumpkin, M., & Hartman, D. (2016). Speeding access to vaccines and medicines in low-and middle-income countries: a case for change and a framework for optimized product market authorization. PLoS One, 11(11), e0166515.

A. **Requirement to develop tailored labels and provide samples for individual countries in advance of authorisation and distribution:** NRAs often request tailored vaccine labels (e.g., translated into local languages) before authorising vaccines in their countries. In addition, they also request sample vaccine vials in advance to confirm labelling requirements are met. Lastly, some NRAs may request vaccine samples for lab testing to conduct basic (e.g. pH test) and advanced (e.g. potency) testing. Fulfilling these requirements for all 55 Member States are questionably value added for versions of products that are SRA authorised and/or WHO EUL or PQ listed, when these tests will have already been performed by the manufacturer and the national authority in the country of manufacture (whose ability to perform such tests will have already been certified by WHO) and may be time consuming to the manufacturer, in a time of extreme global emergency when the manufacturer is receiving multiple requests for product from multiple countries simultaneously. Moreover, country-specific labelling and package may hinder an efficient global vaccine distribution programme by preventing quick diversion of stockpiles to any country[11] where the need is greatest at any given moment.

B. **Requirement to carry out local vaccine clinical trials:** In a survey of African NRAs, 95% noted that, when scientifically justified, they would require local clinical trials to authorise medical products[12]. In the context of COVID-19 vaccine development, however, relatively few COVID-19 vaccine clinical trials have been undertaken on the continent. This means that the requirement might prevent NRAs from approving vaccines that have proven to be safe and effective in clinical trials in other countries, and in similar populations. While there are times where there are scientifically justified reasons for requiring local trials, these must be weighed in view of the risks of the pandemic versus the risk of not knowing some of these local potential risks at the outset of a vaccine distribution programme.

C. **Pre-acceptance requirements for countries:** WHO invites selected NRAs, including from the AFRO region, to participate in the global EUL/PQ dossier evaluation process. These NRAs attend the WHO facilitated sessions and provide their perspectives as they participate in the joint review process. These AFRO and EMRO region representatives at the WHO EUL/PQ dossier evaluation process then can help other NRAs from the same region to better understand the EUL or PQ decision and thus more readily rely on the information from the WHO EUL process in making their final national decision. Therefore, any lack of participation or delays in fulfilling the pre-acceptance requirements by the selected NRAs can become a barrier to the EUL acceptance more widely by those continental national authorities, which did not participate in the WHO EUL or PQ assessment and decision-making process. Furthermore, national NRAs often request additional information during their dossier review process that can cause further delays, and, often any such questions can be discussed quickly with the AFRO and EMRO agencies, which participated in the WHO EUL or PQ process.

[11]Wolf, J., Bruno, S., Eichberg, M. et al. Applying lessons from the Ebola vaccine experience for SARS-CoV-2 and other epidemic pathogens. npj Vaccines 5, 51 (2020).
[12]Africa COVID Regulatory Marketing Authorization Oversight Survey

D. **Delays in acceptance of EUL by NRAs and final approval from MOH or high-level ministries:** NRAs from the 55 Member States will ultimately have to make individual decisions based on the outcome of the SRA and/or WHO EUL joint review process (if the version of the vaccine being shipped to their country is the version assessed by the SRA and/or WHO), including issuing a final decision document, often signed by the Minister of Health and head of the NRA. In the past, there have been significant delays in the administrative processes to issue final decisions and communicating these with manufacturers.

E. **Lack of standardised SRA reliance framework (obtaining necessary documentation from SRA):** Currently, there is no well-established procedure for reliance on emergency use processes by SRAs by African NRAs. This may cause duplication of work and delays in cases where vaccines are approved by SRAs but not through WHO PQ/EUL.

Country-level market authorisation of COVID-19 vaccines

The set of barriers related to obtaining final marketing authorisation in importing countries, immediately after SRA vaccine authorisation and/or WHO EUL or PQ listing, are outlined below:

F. **Requirement for Certificate of Pharmaceutical Product (CoPP) in country of manufacture**: According to a survey of African NRAs, 75% of the NRAs say they will require a CoPP from the country of manufacture[4]. This is often required at the point of submission, and in hard-copy versions only, introducing significant delays into the dossier review process.

G. **Requirement for lab tests/lot release as part of authorisation processes:** 50% of respondents to the African NRAs survey say they will require local laboratory testing of product prior to authorisation and/or importing into the country[4]. Testing of vaccines is time-consuming and requires advanced equipment that can only be managed by specialised labs not present in all African Member States. Considering the limited testing capacity and lack of specialised labs in many African countries, lab testing requirements can drastically slow down vaccine rollout, and divert capacity away from field testing of products already on the local market, which is critical to minimise the risk of counterfeiting.

H. **Requirement for issuance of indemnification for vaccine manufacturers:** Before distributing medical products in a country, manufacturers often require indemnification agreements from importing countries. Indemnification is especially important for emergency use licensed vaccines, which are still undergoing clinical trials. The European Union have agreed to a liability shield for Pharmaceutical companies on any unexpected side effects[13], and the US already had the same policy embedded in the Public Readiness and Emergency Preparedness Act[14]. WHO is also working to address this challenge.

[13]Parliamentary questions, European Parliament (https://www.europarl.europa.eu/doceo/document/E-9-2020-004950_EN.html), 9 September 2020

[14]"H.R.2863 - Department of Defene, Emergency Supplemental Appropriations to Address Hurricanes in the Gulf of Mexico, and Pandemic Influenza Act, 2006: Actions". United States Congress. December 30, 2005.

I. **Requirement for importer certificate of competence and license for each country of distribution:** Vaccine importers often need to be licensed and receive all the necessary authorisations before importing COVID-19 vaccines to a country. UNICEF SD is currently leading the vaccine procurement and supply operation on behalf of the COVAX Facility and will be the primary importer of COVID-19 vaccine in Africa. Therefore, the time it takes to grant import permits and other required authorisation to UNICEF SD and other importers can delay COVID-19 vaccines dispatch to Africa.

J. **Separate use policy statement formulated by each country:** 89% of NRAs in the African NRAs survey noted that a local use policy statement is required before medical products can be authorized[4]. Tailoring of product use policy statements for each country will create delays to the COVID-19 vaccine authorisation timeline.

K. **Lengthy process of customs approval:** Importers usually experience delays in customs clearance caused, in part, by a lack of coordination between NRA and customs authority, as well as a lack of pre-defined emergency custom processing procedures (e.g. pre-clearance or pre-advise). Delays in custom clearance pose a dual risk: the delay of the delivery of the vaccines and breach of the cold chain of these vaccines, thus potentially introducing wastage or use of vaccines whose potency cannot be assured.

L. **Lack of coordination on vaccine approvals across multiple in-country stakeholders:** Multiple country-level stakeholders are involved in the COVID-19 vaccine licensing, importing and immunisation process, including NRAs, MOH, national immunisation program, logistics and supply chain companies and others. Fragmented decision making and lack of effective multi-sectoral information sharing between these stakeholders can cause delays in issuing important decisions and documents.

M. **Lack of coordination in monitoring and evaluating Adverse Events Following Immunization (AEFI):** Countries have separate systems and procedures for drug safety monitoring. This has both capacity and quality implications. Many countries will not have the capacity to manage active monitoring systems (i.e. through surveys of immunised patients), which is more effective than passive systems using voluntary ad hoc reports from practitioners and patients. Moreover, the data available to countries may not capture some adverse events with low incidence, due to the limited size of the samples and insufficient quality data collection methods (i.e., slow and limited existing paper-based data collection through immunisation workers or other health workers). Lastly, the limited in-country analytical tools may make it difficult for MoHs and country regulators to make analyse the relevance of the reported event to the vaccine administration and make decisions regarding continuation or modification of a vaccination programme in the event of significant adverse reactions.

(Footnotes)

[1]Wolf et al. "Applying lessons from the Ebola vaccine experience for SARS-CoV-2 and other epidemic pathogens", npj Vaccines 2020. https://www.nature.com/articles/s41541-020-0204-7

[2]Interviews with Merck SDC

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